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EXAMINER
SPIEGEL,C

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DATE MAILED: 06/10/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on preliminary 6/7/95 1 5/20/96 3 5/28/96 No ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), No days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 6-8, 10 and 13-18 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 1-5, 9 and 11-12 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 6-8, 10 and 13-18 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☒ been filed in parent application, serial no. 08/182,550 ; filed on 1/18/94.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

PRELIMINARY AMENDMENT

The preliminary amendment submitted June 7, 1995 (paper #4) is acknowledged and has been entered. The second preliminary amendment faxed May 20, 1996 (paper #5) is acknowledged but cannot be entered because it does not amend the pending claims and, therefore, is an improper amendment. The third preliminary amendment faxed May 28, 1996 (paper #6) is acknowledged and has been entered. Claims 1-5, 9 and 11-12 have been cancelled. Claims 13-18 have been added. Claims 6, 7 and 10 have been amended. Although the dependency of claims 6, 7 and 10 have been amended without proper bracketing and underlining, these changes have been treated as an inadvertant typographical error. Claims 6-8, 10 and 13-18 are pending.

INFORMALITIES

The disclosure is objected to because of the following informalities: on page 1 (insert A1) update the status of parent application USSN 08/182,550. Appropriate correction is required.

The drawings are objected to for reasons on the accompanying NOTICE OF DRAFTSPERSON'S PATENT DRAWING REVIEW (PTO-948). Correction is required.

REJECTIONS UNDER 35 U.S.C. § 112

Claims 6-8, 10 and 13-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

To provide for proper antecedent basis and consistent language in claim 13, it is suggested that --each of the-- be inserted before "individual" in line 20; and, that "single" in line 21 be deleted and replaced with --each of the individual--. Claim 13 is unclear in reciting "a statistically reliable measurement" without providing guidelines for such reliability, e.g. a coefficient of variation of less than 10%, etc. Claim 13 is apparently contradictory and, therefore, confusing in requiring each individual microparticle to emit a single corresponding to the analyte's concentration in lines 11-18, but then requiring measurement of the minimum number of microparticles that will provide a reliable measurement of the analyte's concentration in lines 19-27. Claim 13 creates confusion as to the relationship between the "statistically reliable number" of microparticles and the "predetermined number" of assay microparticles. The "improvement" step of claim 13 is confusing. It is unclear whether each microparticle is to be measured as a single unit which is directly correlated to analyte concnetration or whether the total summed signal from a known or predetermined number of microparticles are measured in order to determine analyte concentration. It is unclear how the method of claim 1 differs from routine optimization of assay parameters.

It is unclear where the method steps of claims 14 and 15 occur within the method of claim 13; how these added method steps further limit the method of claim 13; and, how "employed" and "used" differ.

Claim 16 is nonidiomatic or, alternatively confusing, in reciting "an antigen of the analyte", in describing a labelled reactant as only consisting of the reactant, and in describing

an unlabelled reactant as comprising more than the reactant. The following language is suggested for applicants' consideration.

> The assay method according to claim 13, wherein the assay is a competitive immunoassay in which the labelled bioaffinity reactant B comprises the analyte or an analog thereof, and the bioaffinity reactant A is an antibody for whose specific binding sites the labelled bioaffinity reactant B and the analyte compete.

See also claims 6 and 7 (e.g. --B comprises an antibody/nucleic acid probe which specifically binds to/hybridizes with the analyte--).

Claim 17 appears inherent in claim 13's requirement of measuring the "minimum number" of individual microparticles. In the alternative, it is unclear how claim 17 further limits claim 13.

The recitation of a single analyte in claim 13 does not provide proper antecedent basis for the multianalyte method recited in claim 18. Therefore, it is suggested that applicants consider amending claim 13 to recite --at least one analyte to be assayed-- instead of "an analyte to be assayed" in line 3, with similar amendments to other parts of claim 13 and to other claims as needed for proper antecedent basis.

Claim 8 depends on cancelled claim 1 and appears to be a substantial duplicate of claim 16. Claim 8 is also confusing in reciting "characterized".

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure and failing to provide an adequate written description of the invention.

The specification fails to teach or suggest how to reproducibly and predictably adjust the amount of sample volume and composition of microparticles so as to allow the measurement of analyte concentration over the whole range of typical analyte concentrations by separate measurement of each individual microparticle as recited in claim 13.

The specification fails to provide guidance for relating analyte concentration range to the quantity of binding sites needed *per se* in terms of either the solid phase bioaffinity reactant or the labelled bioaffinity reactant (e.g. sufficient solid phase antibody to bind 33% of the labelled antigen in the absence of unlabelled antigen; or, some other defined target analyte-solid phase specific binding member fractional occupancy relationship, etc.) or to the type of signal generating system used. Rather, the specification suggests that each combination of analyte concentration range, specific binding partner, size of microparticle, label, detection system (e.g. time-resolved), etc. has to be empirically determined for each assay. Thus, undue experimentation would be required to ascertain not only the predetermined number of microparticle bound reactants, but also the number of individual microparticles necessary to correlate to analyte concentration. Furthermore, it appears that the

specific binding assay reaction(s) must be allowed to reach equilibrium before measurements of individual microparticles may be taken.

The specification fails to provide an adequate written description of "the DELFIA assay solution" used to exemplify a typical measurement system/technology. The specification fails to provide an adequate written description of the "the sensitive label technology", e.g. detection limits, number of label molecules per conjugate, etc.

How the claimed invention differs from routine optimization of the assays of the prior art is unclear from the specification. Conventional specific binding reactions using conventional solid phase and labelled binding partners in conventional competitive or sandwich assay formats are being used. In the sandwich format, e.g. a conventional excess of solid phase reactant over expected analyte concentration is used to capture as much analyte from the test sample as possible. However, routine optimization suggests using as small an excess of solid phase reactant as possible to prevent unnecessary "diluting" the signal of later bound labelled reactant. It is unclear how the claimed invention differs.

Lastly, it is unclear how the "wet"/"dry" differentiation in Fig. 1 relates to Example 1.

Claims 6-8, 10 and 13-18 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

REJECTIONS UNDER 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 6, 8, 10 and 13-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Soini et al. (US 5,028,545) alone or as necessary further in view of either Ekins et al. (*Clinical Chemistry* 37(11):1955-1967, 1991) or Buechler et al. (US 5,089,391).

Claim 7 is rejected under 35 U.S.C. § 103 as being unpatentable over the above references as applied to claim 13 above, and further in view of Bush et al..

Soini et al. describes high detection sensitivity biospecific assay methods using time-resolved fluorescent tracers and microparticles coated with analye specific bioaffinity reactants using flow cytometry and microfluorometric measurement systems (col. 1, lines 27-56; col. 2, lines 20-37). Soini et al. differs in failing to disclose explicitly, basic concepts used to

optimize biospecific assay methods, i.e. the interrelationship between sample analyte and assay reactants used to provide maximal sensitivity as instantly claimed.

Ekins et al. teaches all immunoassays rely on the measurement of antibody (i.e. bioaffinity reactant A) occupancy by analyte. Ekins et al. further teaches there are two schools of thought for optimizing biospecific assay methods based upon occupancy -- i.e. the Yalow-Berson school which maximizes sensitivity by using an amount of antibody that binds 33% of labeled antigen in the absence of unlabelled antigen; and, the Ekins et al. school which holds that when the amount of antibody is vanishingly small (i.e. amount of microparticles used), fractional antibody occupancy is independent of both the amount of antibody concentration and sample volume. While Ekins et al. exemplifies adjustment of antibody concentration and sample, i.e. analyte, concentration to optimize a microspot immunoassay, Ekins et al. explicitly comments on the generic applicability of the teachings therein (see the entire article).

Buechler et al. is in the Yalow-Berson school and teaches optimization of the concentrations/volumes of receptors, tracers and analytes to provide signal generation at predetermined levels of analyte concentrations.

Bush et al. is added to show the applicability of time-resolved fluorescent labelled microparticle based assays to hybridization formats.

Therefore, minus a showing of unexpected results, it would have been obvious to combine the generic optimization procedures of either the Yalow-Berson school (e.g. seen in

Buechler et al.) or the Ekins et al. school in any given biospecific assay method, such as the fluorescent labelled microparticle based assay of Soini et al. or Bush et al., in order to obtain maximum sensitivity and/or minimize random errors as suggested by Ekins et al. and Buechler et al. In addition, one of ordinary skill in the art would have considered at least the following factors in optimizing a given biospecific assay: the expense of bioaffinity reagents, the clinically (or otherwise) significant result range, the type of sample being assayed, the desired time to result, etc.

REMARKS

To the extent applicants reiterated the arguments in the parent case, the rebuttals thereto are also reiterated by incorporation. More specifically, the May 28, 1996 response argues

> In the conventional non-competitive immunoassay, all the analyte molecules in a fixed sample volume are attached to the immobilized antibody. In the occupancy method (Ekins) only a fraction of the analyte molecules is attached to the immobilized antibody, wherein the amount of bound fraction is dependent only on the analyte concentration in the sample (according to the law of mass action) and independent of the amount of sample.

(see page 5, second paragraph).

It is clear that this statement serves to differentiate the Yalow-Berson school from the Ekins et al. school. It is unclear how this argument relates to the claimed invention. There are no claimed limitations to the relationship between the predetermined number of

microparticle reagents used and the analyte in the sample, e.g. Since this argument is not commensurate in scope with the claimed invention, it is not persuasive.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Lindmo et al. (US 4,408,877) describes a flow cytophotometer device.

Frengen et al. (*Clinical Chemistry* 39(10):2174-2181, 1993) describes a homogeneous immunofluorometric assay of α-fetoprotein with macroporous, monosized particles and flow cytometry. The use of flow cytometry facilitates homogeneous particle-based assays because only negligible amounts of medium fluorescence are excited from the single-particle sensing volume of the flow cytometer. Frengen et al. also assumed the particle concentration to be rate limiting.

Christopoulous et al. (*Clinical Chemistry* 36(8):1497-1502, 1990) describes an ultrasensitive time-resolved fluorescence method for determining α-fetoprotein.

Ekins et al. (US 5,516,635) describes binding assays using labelled reagent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carol A. Spiegel whose telephone number is (703) 308-3986.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Carol A. Spiegel
May 29, 1996

Carol A. Spiegel

CAROL A. SPIEGEL
PRIMARY EXAMINER
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